IN The Name Of GOD

Mesenchymal Stem Cell Homing in Wound Healing

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Qazvin University of medical Sciences

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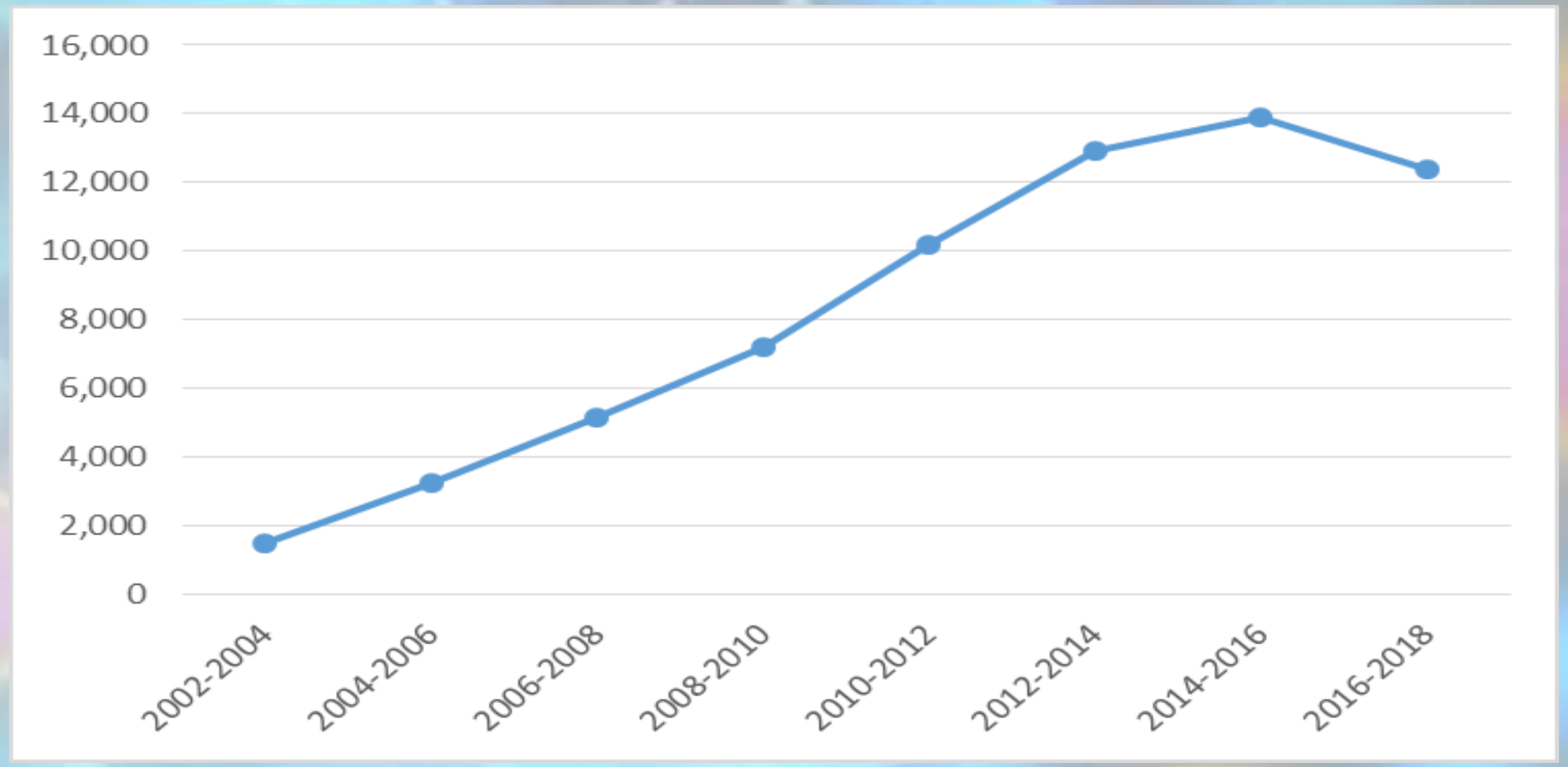
Content

Historical developement



Google scholar

Wound

- USA → 6 million ($25 billion annually)
- Europe → 2% of health budgets (1,۲)
- Iran → 4% of health budgets (3)

Wound Healing

- complex biological process
- restoration of tissue integrity.
- four phases:

1.haemostasis,

2.inflammation

3.proliferation ,

4.tissue remodeling(4)

Wound Healing

Wound Healing

A variety of methods:

- primary intention,
- secondary intention
- tertiary intention,
- skin grafts, and flaps
- Cell therapy

Cell Therapy

- Autologous cells
- Simple
- Less time-consuming
- Reduces the surgical burden
- Not permanently
- Migration and proliferation of host cells

Cell Therapy

APPLICATION OF CELLS

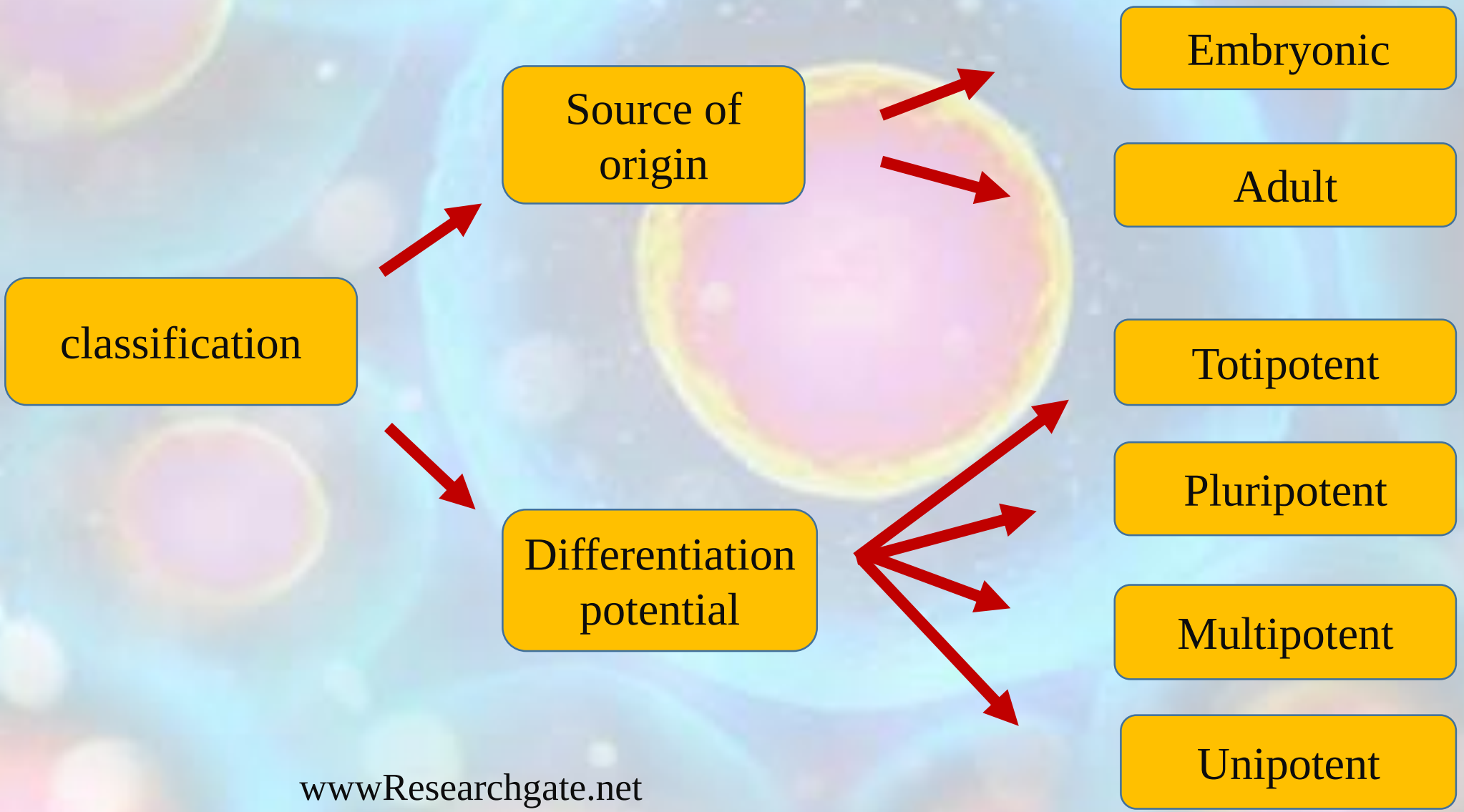
- Keratinocytes
- Fibroblasts
- adipose-derived stromal vascular fraction cells
- Platelets
- Stem cell(5)

Stem cell

Characteristics

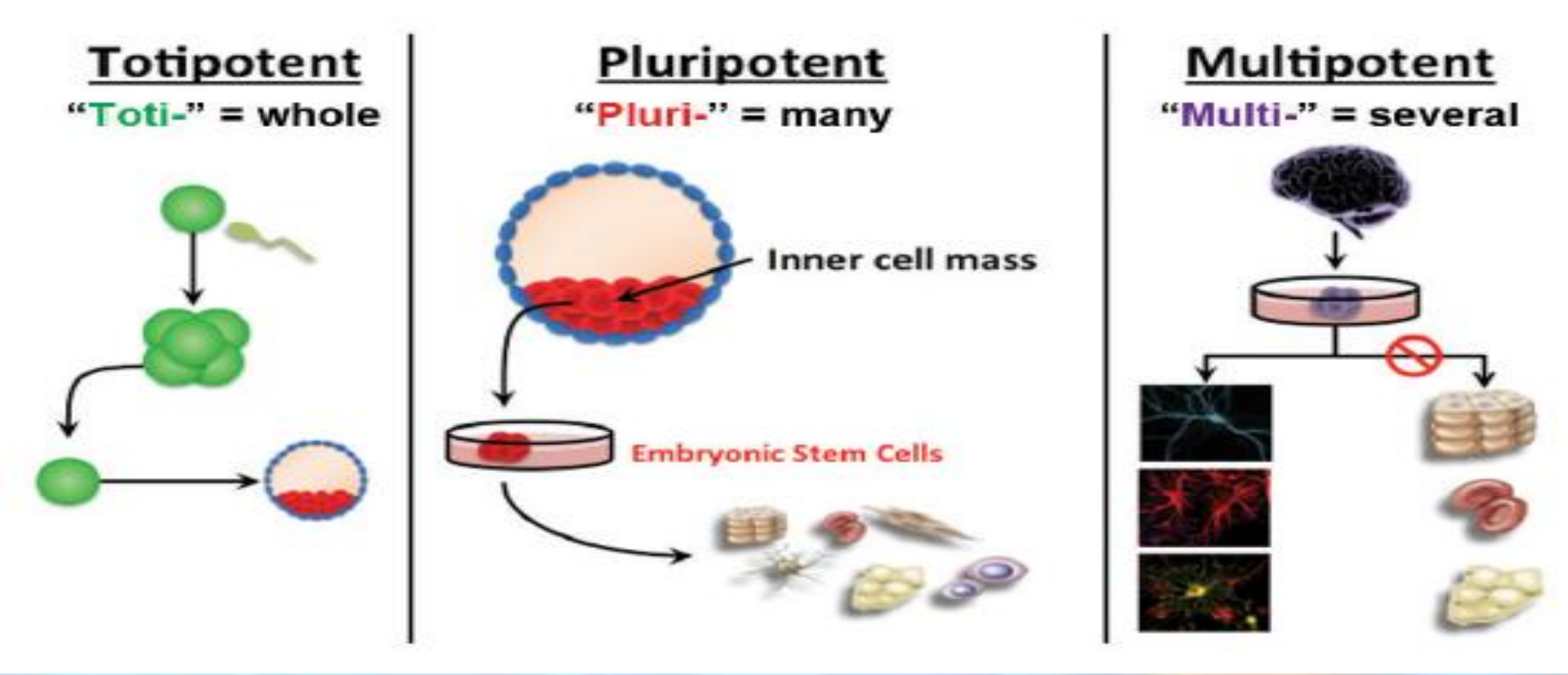
- foundation cells for every organ and tissue.
- Throughout our lives
- replace injured tissues, skin, hair, blood every day.
- self-renew
- Differentiate(6)
- Clonogenic(7)

Stem cell



Stem cell

Classification



Stem cell

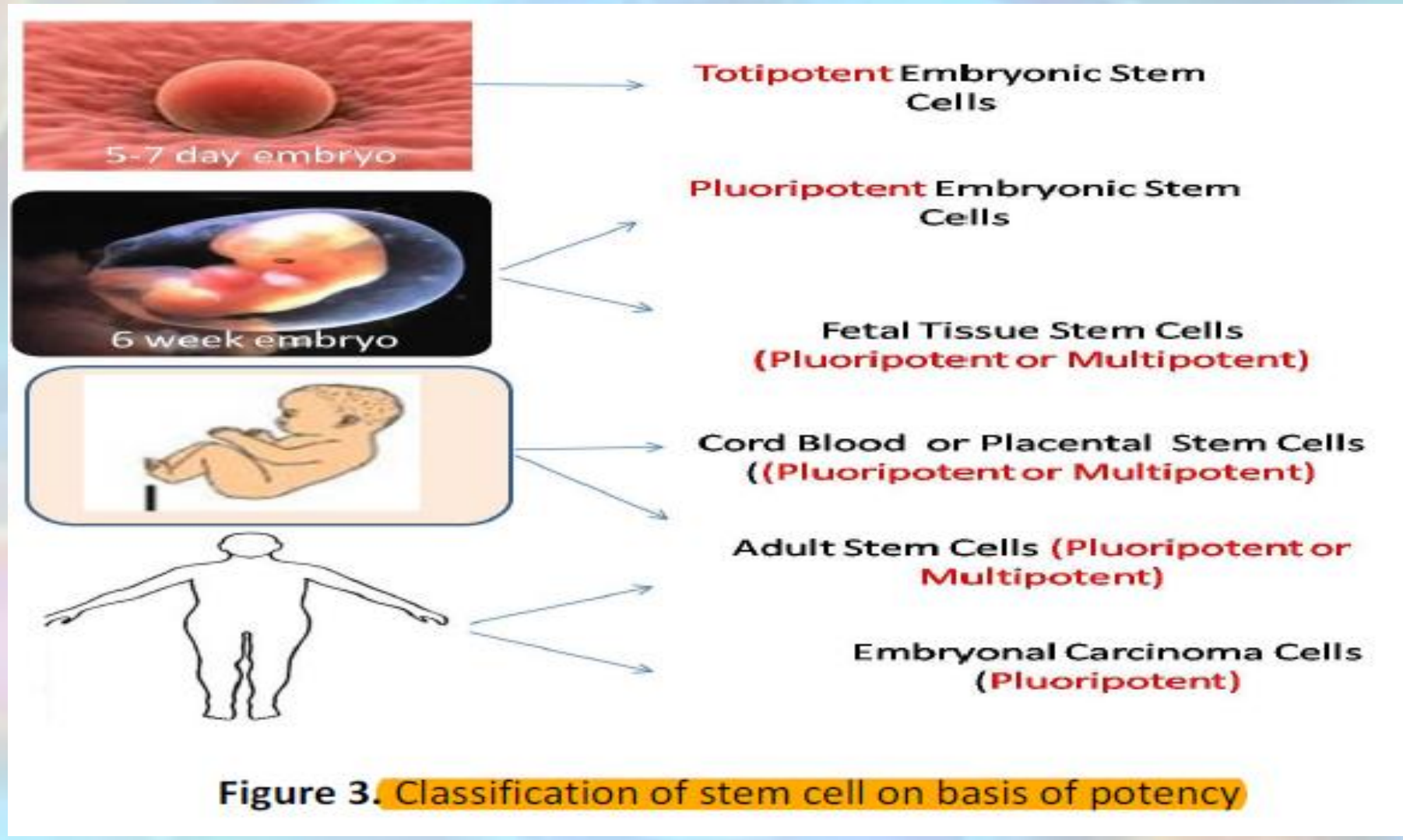
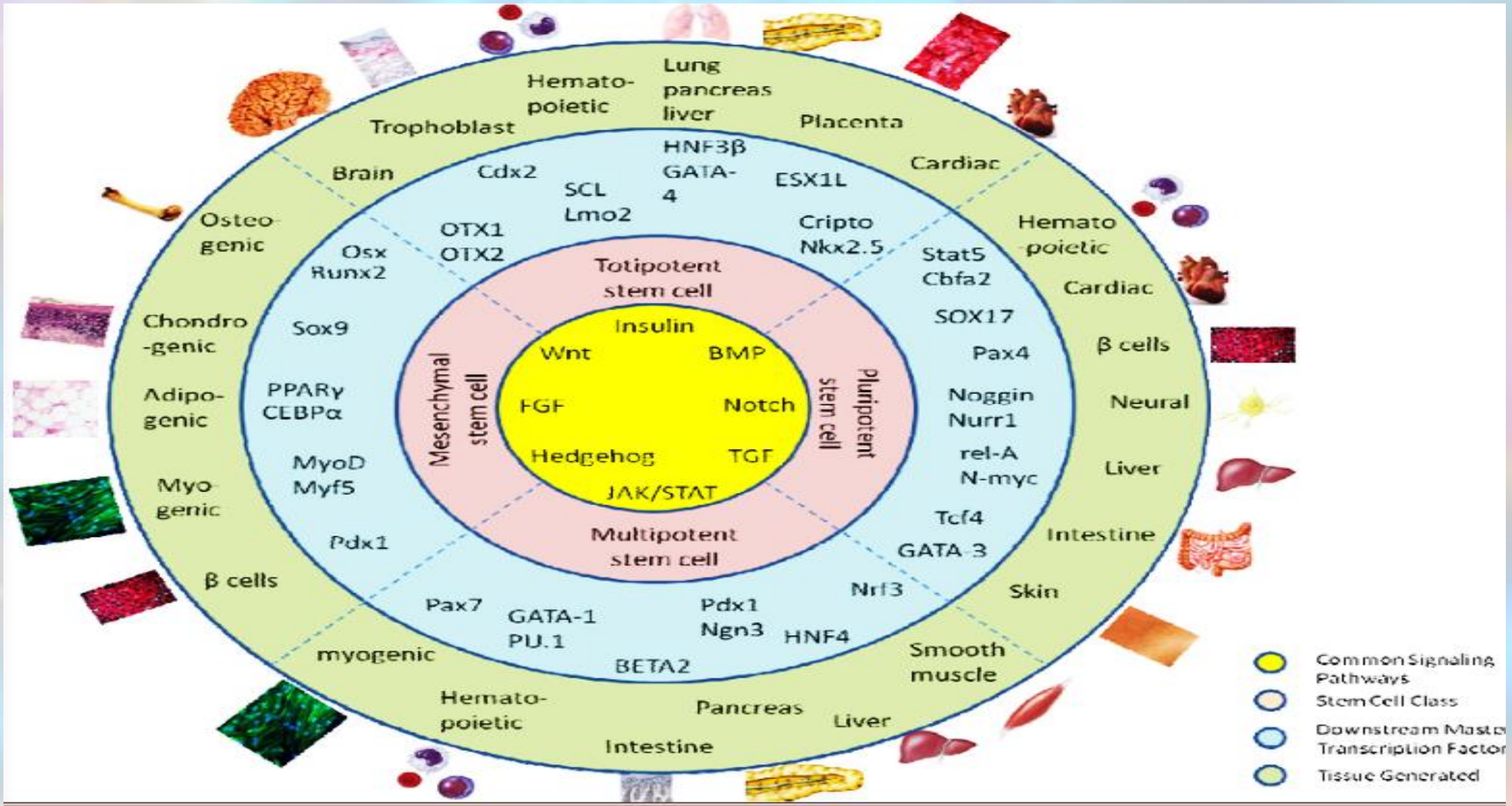


Figure 3. Classification of stem cell on basis of potency

1. Kalra K, Tomar P. Stem cell: basics, classification and applications. American Journal of Phytomedicine and Clinical Therapeutics. 2014;2(7):919-30.

Stem Cell



Clinicaltrials.gov, accessed: 28/3/2013)

Stem cell

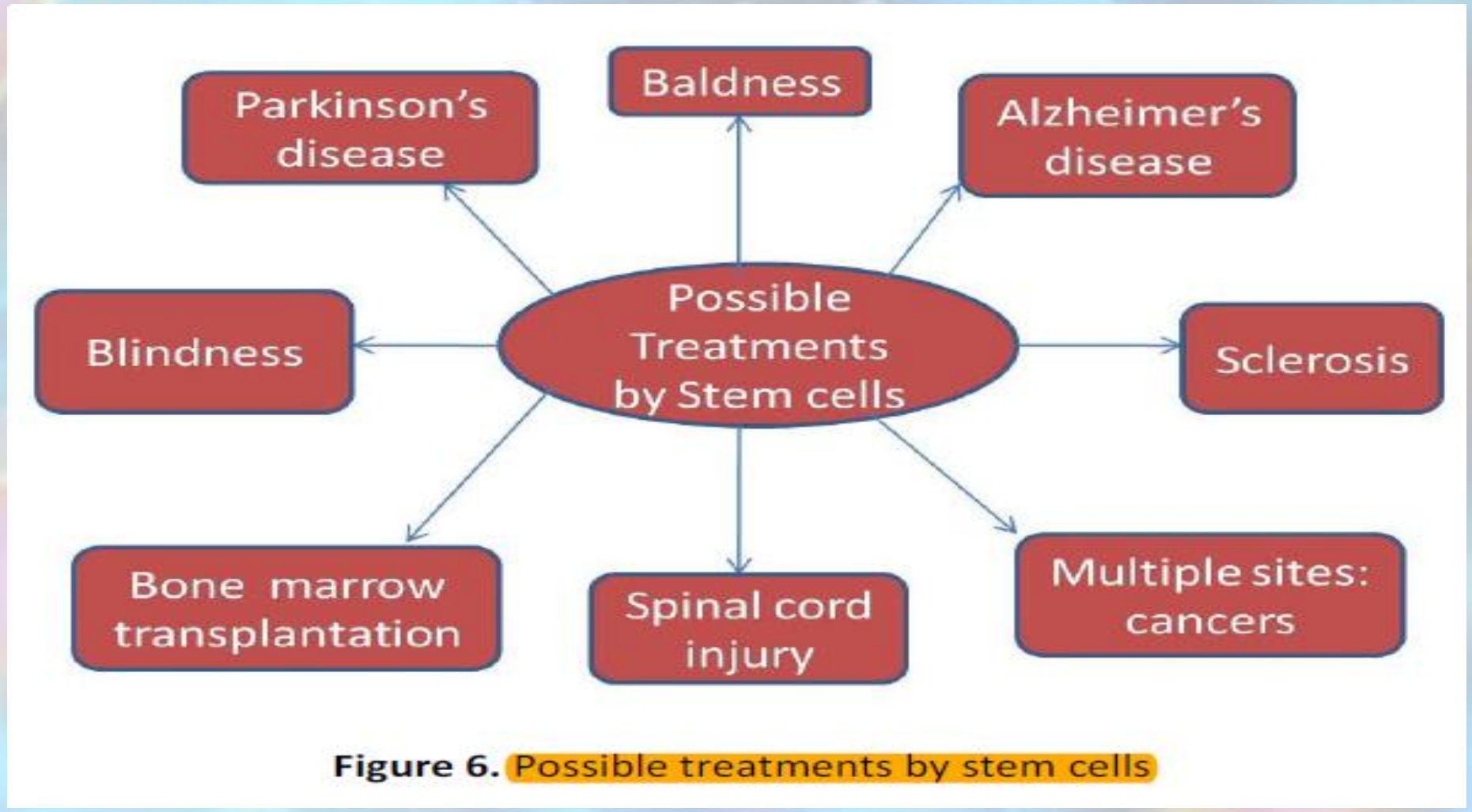


Figure 6. Possible treatments by stem cells

Stem Cell

Mesenchymal Stem Cells(Msc)

- Friedenstein in 1966.

✓spindle-shaped

✓clonogenic cells in monolayer cultures

✓colony-forming unit fibroblasts (CFU-Fs)

- Caplan(1991)

✓first considered as stem cells

✓Named MSCs

Mesenchymal stem cells (MSCs)

- marrow stromal cells
- self-renewing population of multipotent cells.
- to differentiate into diverse mesodermal cell types.

including osteoblasts, chondrocytes and adipocytes

- bone marrow and many other adult tissues.(8)
- in utero MSC transplantation(9)

Mesenchymal stem cells (MSCs)

- Most preferred Stem cells for clinical application

✓convenient isolation

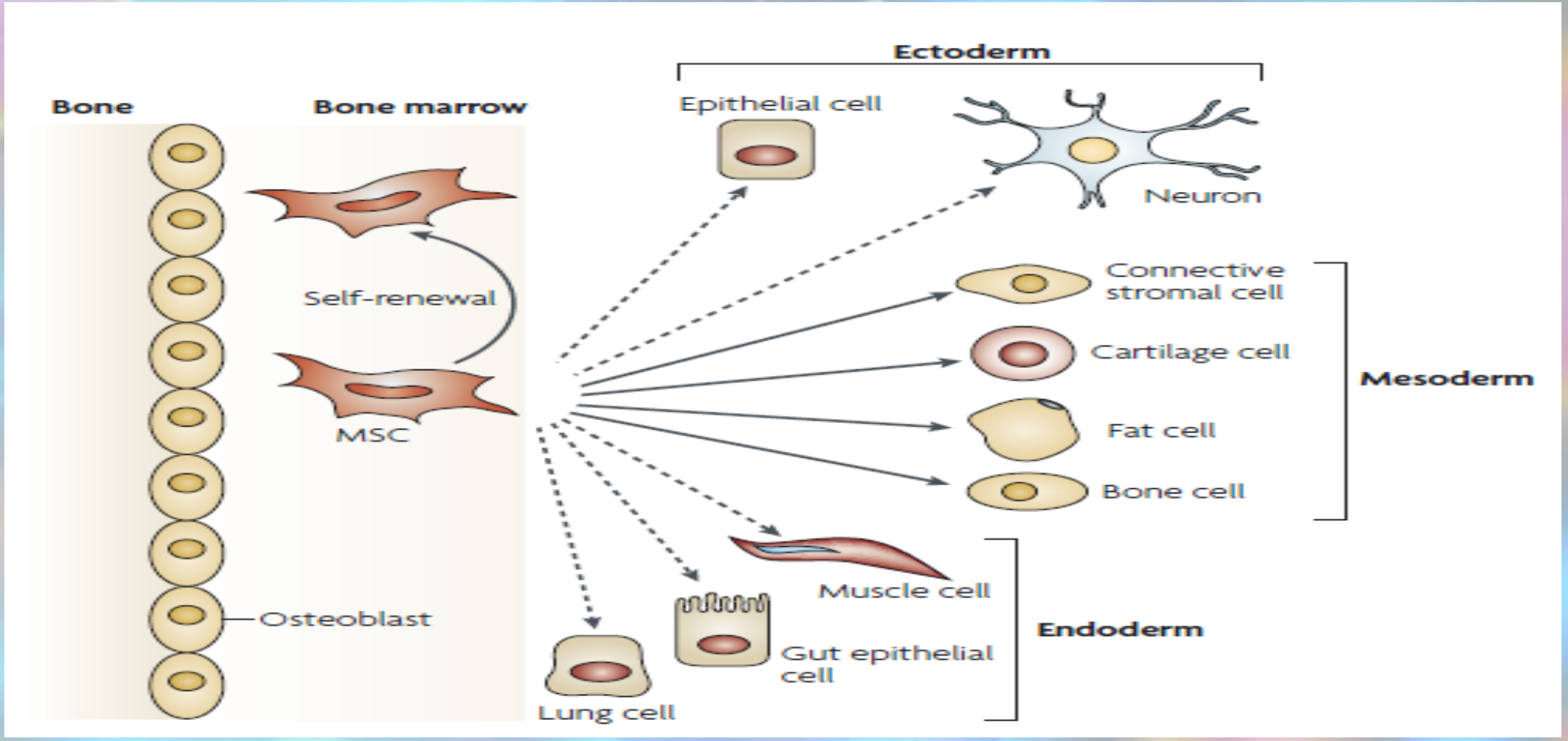
✓lack of significant immunogenicity

✓lack of ethical controversy

✓potential differentiate(10)

- repair of bone
- Support hematopoiesis
- gene therapy vehicles(11)

Mesenchymal stem cell



Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nature reviews immunology. 2008;8(9):726.

Mesenchymal Stem cell

- plastic-adherent cells
- lack specific and unique markers

✓express CD105, CD90 and CD73

✓lack expression of CD45, CD34, CD14 or CD11b,

✓CD79alpha or CD19 and HLA-DR surface molecules(ٰ)

- Immunomodulatory capacities(12,8)
- deliver anti-cancer treatments because home to tumour sites
- regenerative wound healing(12)

Msc in Wound Healing

- key to regenerative wound healing.
- orchestrate wound repair by:

1.structural repair via cellular differentiation

2. immune-modulation

3. secretion of growth factors (neovascularization and repithelialization)

4. mobilization of resident stem cells(homing)(13)

Msc Homing

Homing Definition

- the delivery of the cells to the site of injury.(14)
- the arrest of MSCs within the vasculature of a tissue followed by transmigration across the endothelium(10)
- problem in the field of cell-based therapies.(14)

Msc Homing

History

- first studies → the origin of the bone marrow MSCs after allogeneic bone marrow transplantation
- MSC transplantations in animal models:

✓donor-derived non-haematopoietic cells were present

in the bone marrow, thymus, spleen and liver

- Devine et al and Chapel et al:

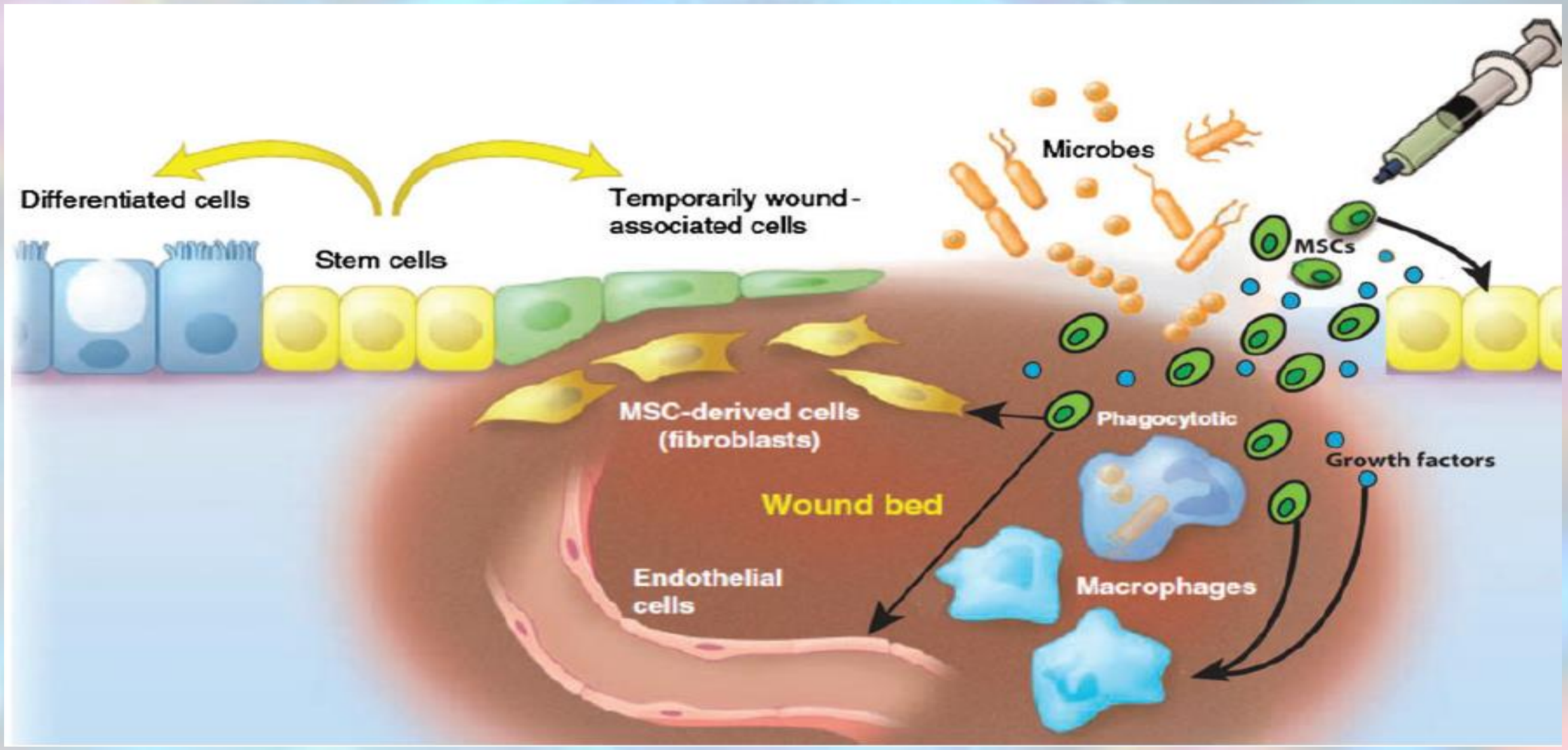
✓MSC transplantations in non-human praimtes.

✓MSCs in a variety of tissues.(0.1% and 2.7%)

Msc Homing

- Erices et al
- described the homing and
- survival of human cord blood derived MSCs in the bone marrow of immunodeficient (nude) mice after systemic infusion

Msc Homing



Balaji S, Keswani SG, Crombleholme TM. The role of mesenchymal stem cells in the regenerative wound healing phenotype. Advances in wound care. 2012;1(4):159-65

Msc Homing

The study of homing, is complex because:

1. lack of universally accepted criteria

- defining the MSC phenotype
- their functional properties

2. rare presence of MSCs within blood.

3. diverse methods used to culture MSCs(10)

Msc Homing

Critical questions

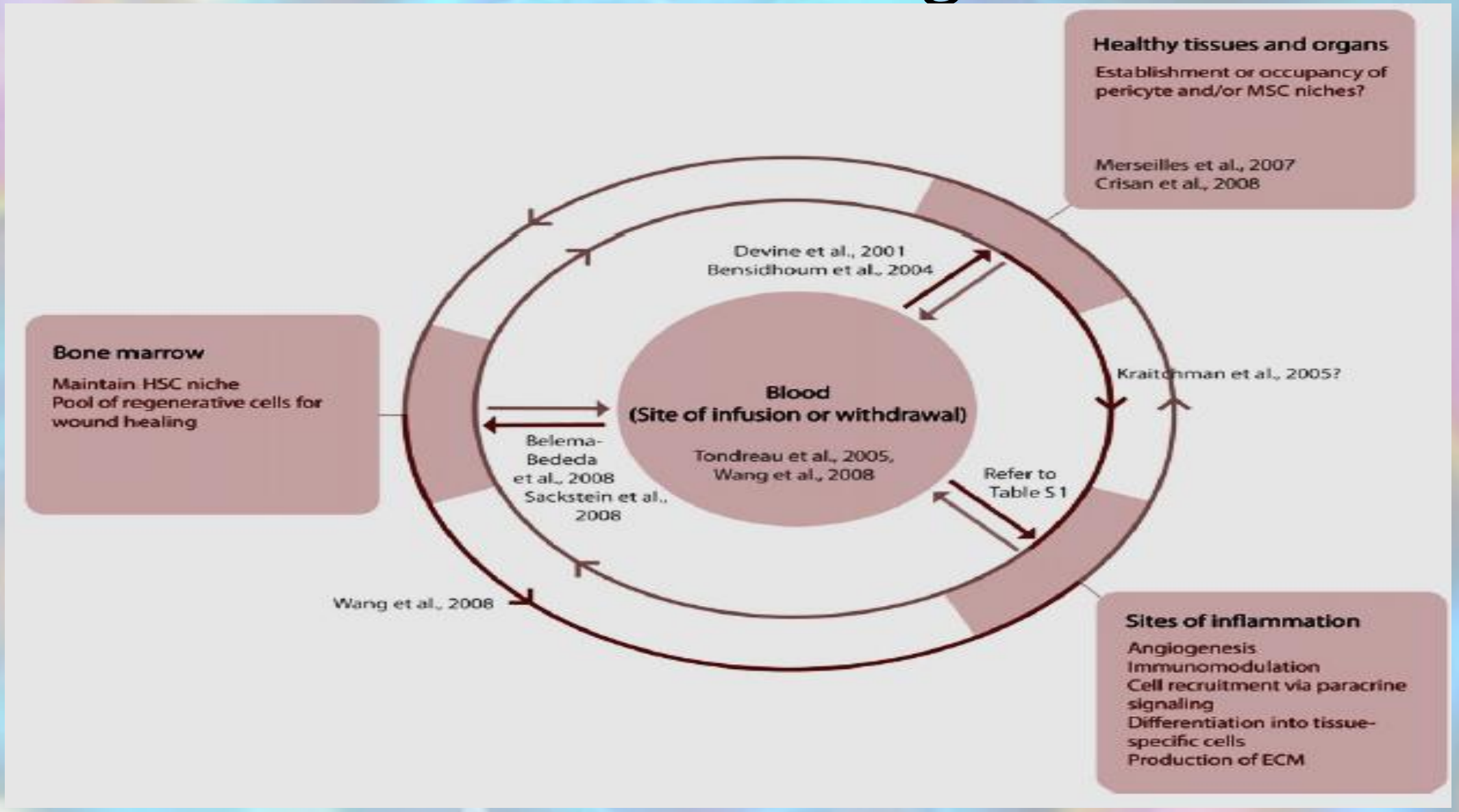
1) host MSCs → ? → peripheral blood

2) exogenous MSCs → ? → ischemic tissues

exogenous MSCs → peripheral blood → ? → Inflammation

3) host MSCs → ? → peripheral blood → ? → target ischemic tissues(10)

Msc Homing



Karp JM, Teo GSL. Mesenchymal stem cell homing: the devil is in the details. Cell stem cell. 2009;4(3):206-16.

Msc Homing

Mechanism

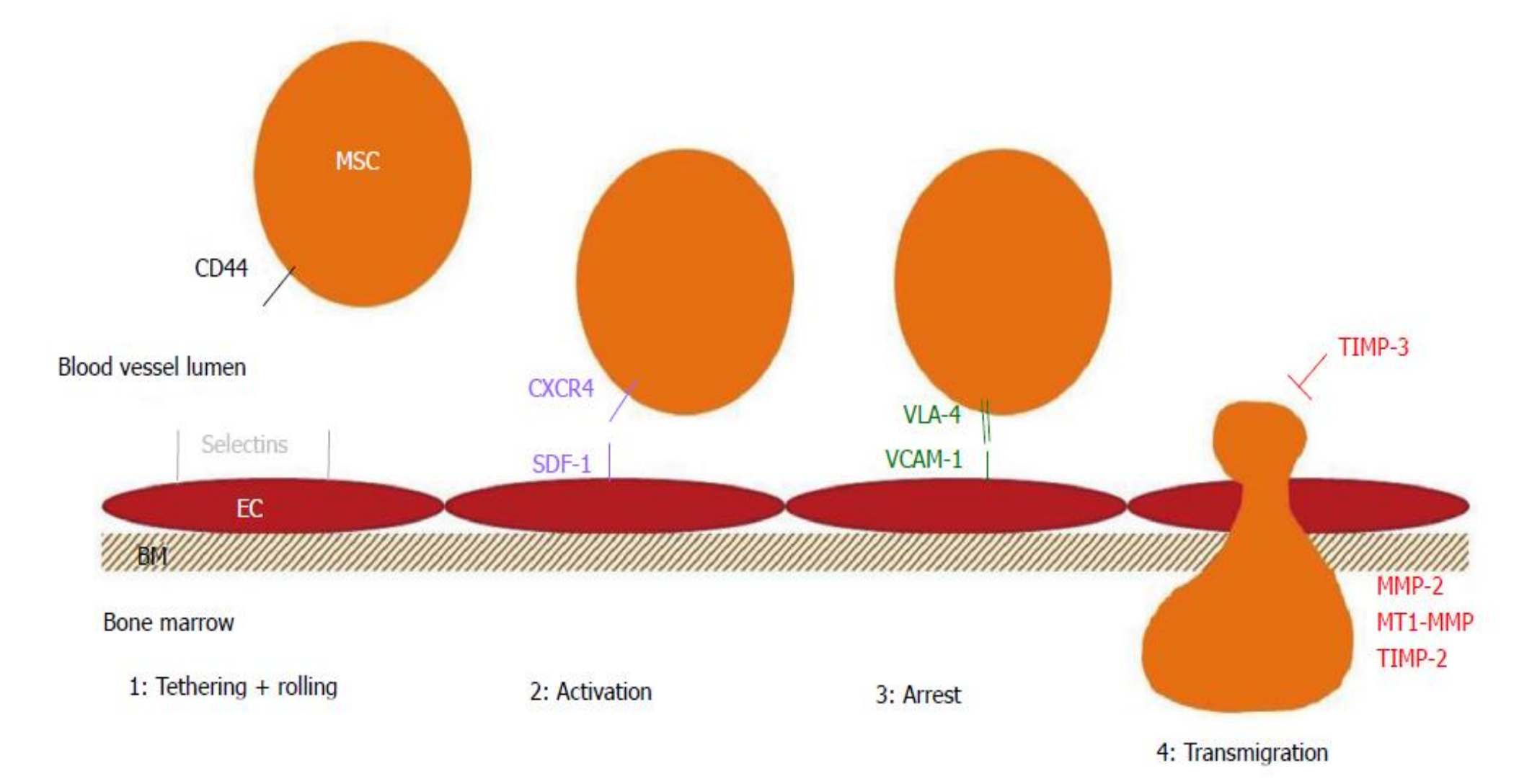
- first step: CD44 and selectin
- Second step: The G-protein coupled receptors activate chemokine receptors.

  CXCR4-stromal derived factor-1 (SDF-1)
- third step: Integrins

  Integrin 4α +β1 → VLA-4 (very late antigen 4) → VCAM-1

  (vascular cell adhesion molecule 1) (15)

Mechanism



Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? Ann De Becker, Ivan Van Riet2016

Homing Msc

Mechanism

- final step : MMP-2 and MMP-9

  Degrade collagen and gelatin

Regulating

- MMP-2
- TIMP-3(tissue inhibitor of metalloproteinases 3)
- MT1-MMP(Membrane type 1 MMP)
- ProMMP-2 + MT1-MMP + TIMP-2 → MMP2*
- ProMMP-2 + TIMP-1 → MMP2 Inactive

Homing Msc

Regulating

1. PDGF(platelet-derived growth factor)
2. HGF(hepatocyte growth factor)

- induce MSC migration.
- gels or scaffolds for improve the in vitro migration(15)

Homing Msc

	Molecules	Migration stage	References
Adhesion molecules	VLA-4, VCAM-1, ICAM-1, P-selectin	Rolling and transendothelial migration	(16-17)
Chemokines/receptors	IL-8, MIP-1α, MCP-1, SDF-1 ,CCR1/2/4/6/8/9 CXCR1/2/3/4/5/6	Chemotaxis and traffic	18
Cytokines/growth factors	TGF-β, TNF-α, IL-1β, IL-6, IL-3, FlT3-L, IGF-1, SCF, HGF, PlGF, PDGF	Chemotaxis and traffic	19
Matrix metalloproteinases	MMP-1, MMP-2	Invasion	20

Msc Homing

multiple factors:

1.Age, Passage Number, and Dosage of MSCs

↑ passage number → the engraftment efficiency of MSCs ↓

↑ Age → potency of resident stem/progenitor cell ↓

Msc homing

- multiple factors:

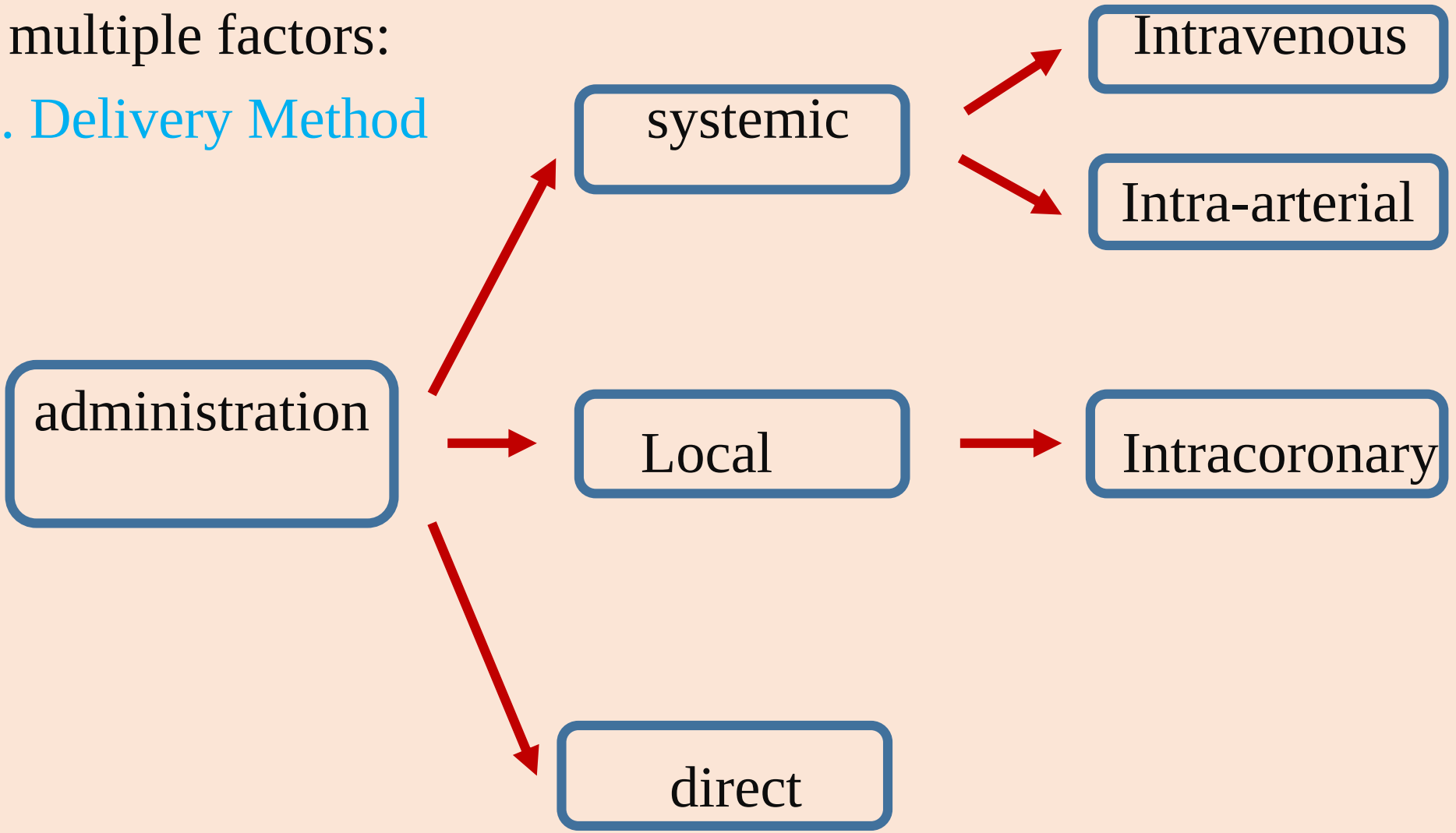
2. Source and Culture Conditions of MSCs

- Multiple different tissues → differences in the phenotype (challenge)
- International Society for Cellular Therapy (ISCT)
- freshly isolated MSCs home better(↓ CXCR4 chemokine Receptor)
- matrix metalloproteases (MMPs)(14)

Msc Homing

- multiple factors:

3. Delivery Method



Msc Homing

multiple factors:

3. Delivery Method

- IV injection is the most widely used:
- minimally invasive
- can be readily repeated
- the oxygen and nutrient rich vasculature
- IV injection → lungs → target tissues

Msc Homing

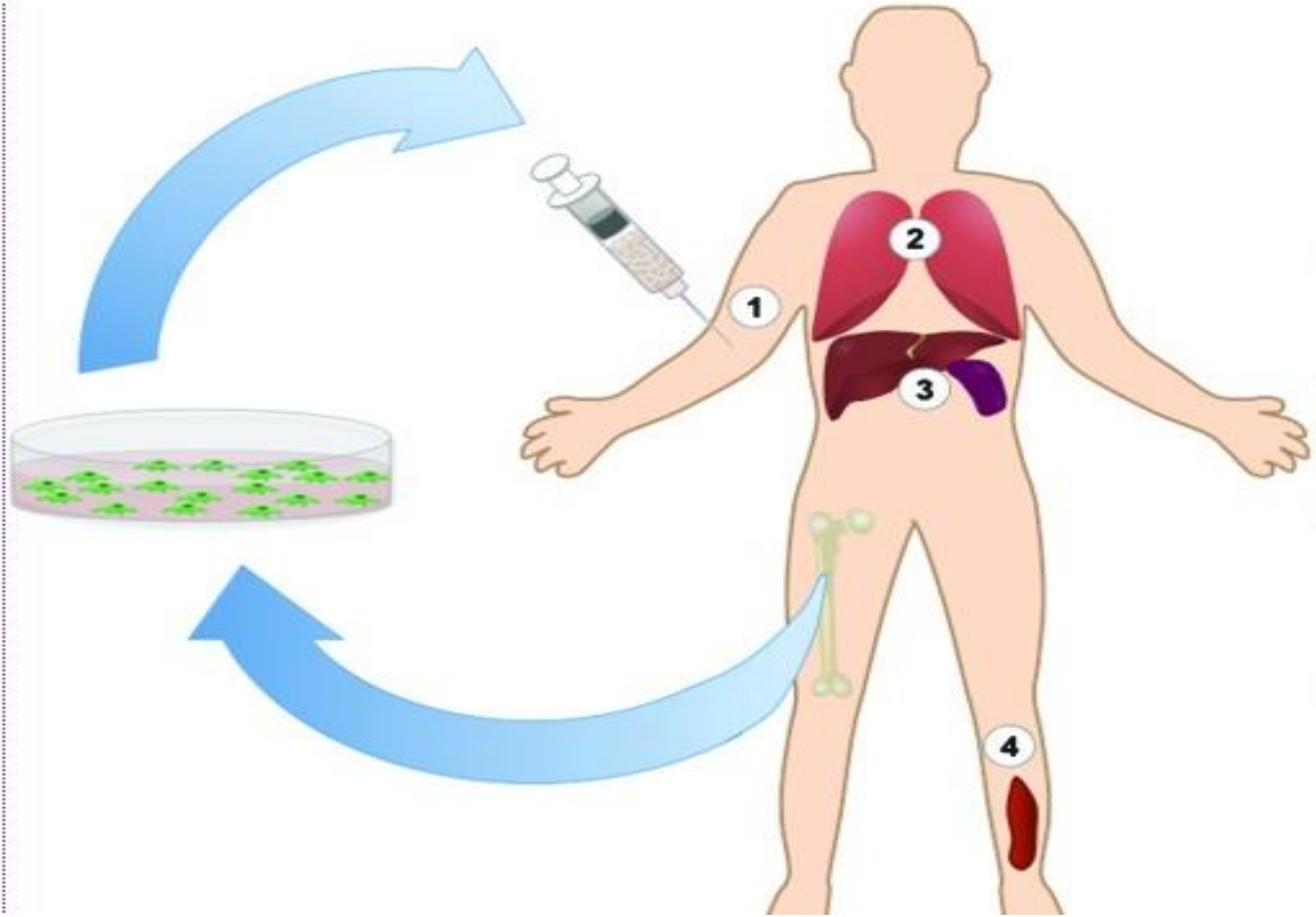
multiple factors:

3. Delivery Method

- IA compared to IV:

✓higher risk complication

✓tissue-specific homing but microthrombi(15)



Dynamic Path of Injected MSCs

1. MSCs are isolated either autogenously or from a donor, expanded *ex vivo* and injected intravenously into a patient
2. During the first few days post-injection, MSCs are primarily entrapped within the lungs
3. One to three days after injection, MSCs begin to exit the lung and also are found within the liver, spleen and other organs
4. In a patient with a wound, following the initial lung entrapment MSCs traffic to the site of injury. MSC homing occurs in response to gradients of inflammatory mediators.

Mesenchymal Stem Cells Home to Sites of Injury and Inflammation. Kristine C.2011

Msc Homing

multiple factors:

4. Host Receptability-Injury versus Noninjured

- low immunogenicity
- chemo-attractants
- genetically engineered
- Vasodilator(14)

Msc Homing

How Can We Improve The Homing Efficiency Of Mscs?

- only a small proportion of a MSCs remains in the target tissue.

✓Limited expression of homing molecules on MSCs

✓lose the expression of homing molecules during in vitro expansion

✓different expression profile of homing molecules

Approaches

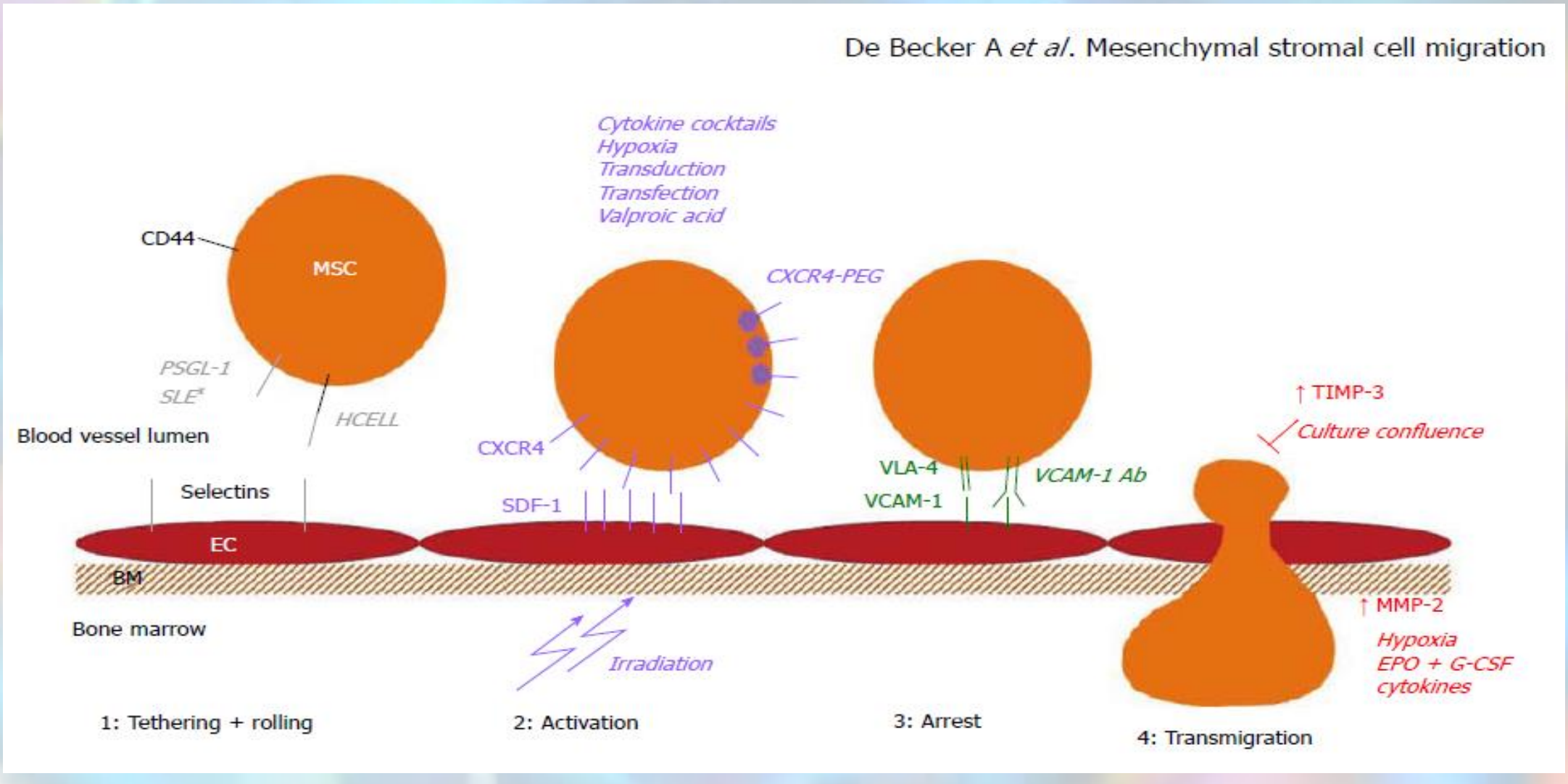
1. Modification of the mode of administration
2. changing culture conditions
3. Genetic modifications

Msc Homing

Approach

4. Cell surface engineering
5. Modification of the target tissue(14)

Msc Homing


De Becker A *et al*. Mesenchymal stromal cell migration
Cytokine cocktails
Hypoxia
Transduction
Transfection
Valproic acid
CD44
MSC
PSGL-1
SLE
HCELL
Blood vessel lumen
Selectins
EC
BM
Bone marrow
CXCR4
CXCR4-PEG
SDF-1
Irradiation
VLA-4
VCAM-1
VCAM-1 Ab
↑ TIMP-3
Culture confluence
↑ MMP-2
Hypoxia
EPO + G-CSF
cytokines
1: Tethering + rolling
2: Activation
3: Arrest
4: Transmigration

JAM-A promotes wound healing by enhancing both homing and secretory activities of mesenchymal stem cells

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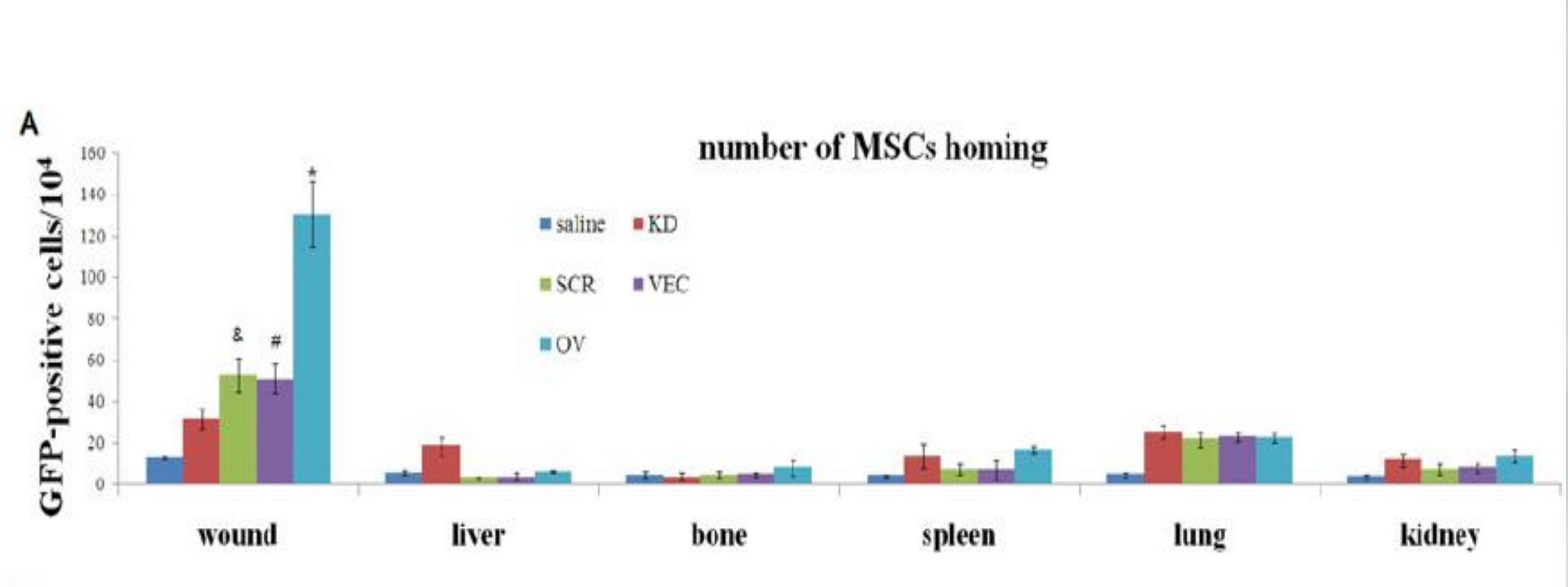
Abstract

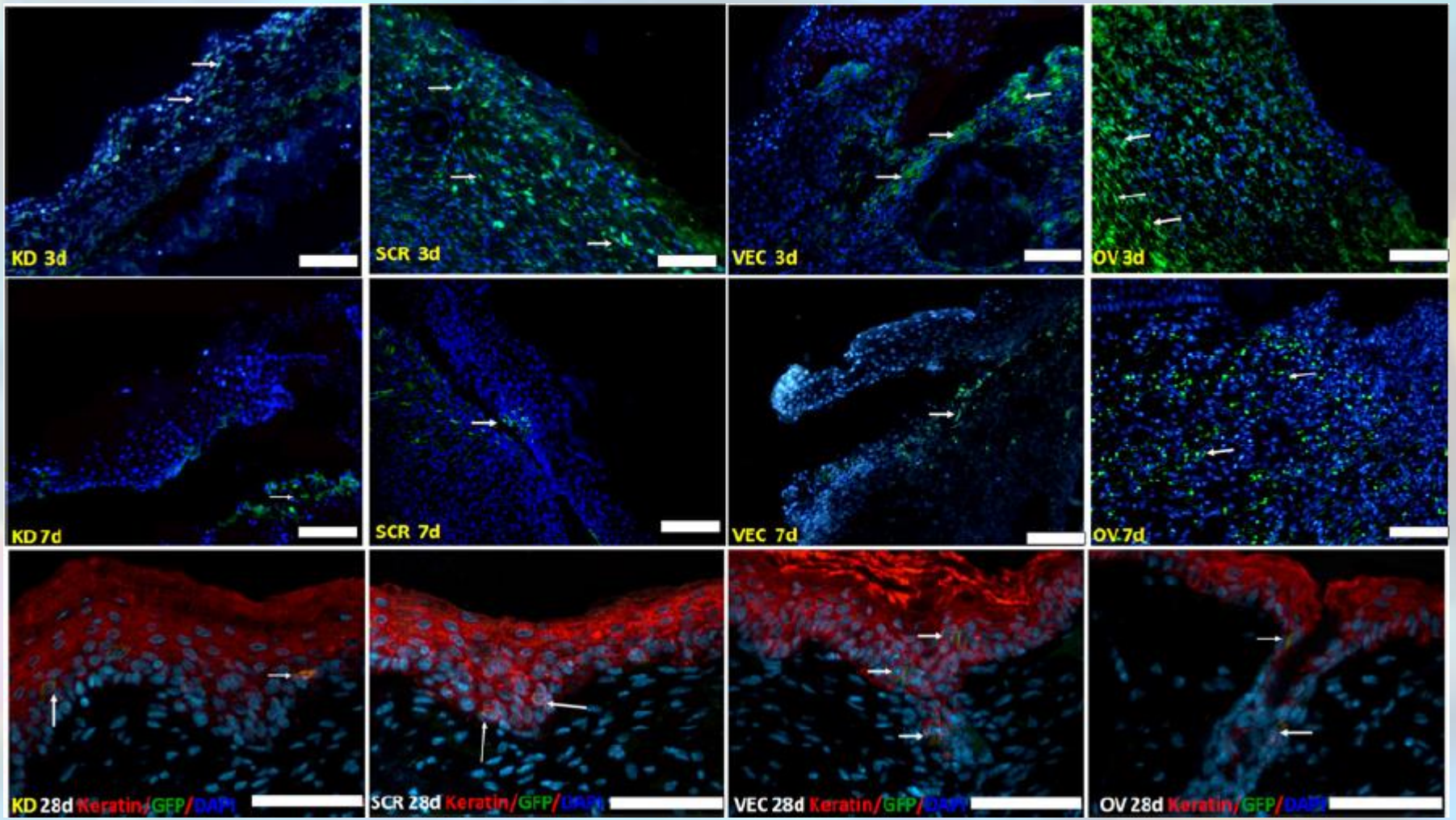
The homing ability and secretory function of mesenchymal stem cells (MSCs) are key factors that influence cell involvement in wound repair. These factors are controlled by multilayer regulatory circuitry, including adhesion molecules, core transcription factors (TFs) and certain other regulators. However, the role of adhesion molecules in this regulatory circuitry and their underlying mechanism remain undefined. In the present paper, we demonstrate that an adhesion molecule, junction adhesion molecule A (JAM-A), may function as a key promoter molecule to regulate skin wound healing by MSCs. In *in vivo* experiments, we show that JAM-A up-regulation promoted both MSC homing to full-thickness skin wounds and wound healing-related cytokine secretion by MSCs. *In vitro* experiments also showed that JAM-A promoted MSC proliferation and migration by activating T-cell lymphoma invasion and metastasis 1 (Tiam1). We suggest that JAM-A up-regulation can increase the proliferation, cytokine secretion and wound-homing ability of MSCs, thus accelerating the repair rate of full-thickness skin defects. These results may provide insights into a novel and potentially effective approach to improve the efficacy of MSC treatment.

Msc Homing



JAM-A promotes wound healing by enhancing both homing and secretory activities of mesenchymal stem cell Minjuan Wu∗†,2015

Msc Homing



JAM-A promotes wound healing by enhancing both homing and secretory activities of mesenchymal stem cell Minjuan Wu∗†,2015

Future Developement

- Genetic engineering
- current medical and surgical interventions for wound(21)
- Understanding exact mechanism improve future MSC-derived therapies(22)
- studies would benefit from a better understanding

  of MSC biology.
- A better understanding of MSC homing, allow researchers to optimize the migration capacities.(15)

Abbreviation

- CD: Cluster of differentiation;
- EC: Endothelial cell
- BM: Basement membrane
- HCELL: Hematopoietic cell E-/L-selectin ligand
- PSGL-1: P-selectin glycoprotein
- ligand-1; SLEX: Sialyl Lewis X
- SDF-1: Stromal cell derived factor 1
- VLA-4: Very late antigen 4
- VCAM-1: Vascular cell adhesion molecule 1
- Ab: Antibody

Abbreviation

- TIMP:Tissue inhibitor of metalloproteinases
- MMP: Matrix metalloproteinase;
- EPO: Erythropoietin
- G-CSF: Granulocyte colony stimulating factor
- MSC: Mesenchymal stromal cell.(15)

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